retically, total body energy content could be maintained at a constant level by regulating the magnitude of food intake, physical activity, or arterial work and heat production. Control of food intake is thus a major determinant of total body energy balance. The level of physical activity is primarily under voluntary control, and mechanisms that alter the degree of arterial work and heat production are under primarily controlling body temperature rather than total energy balance.

However, after several weeks of eating less or more than desired, compensatory changes in metabolism may occur. For example, a compensatory increase in the body's expenditure of energy in response to underfeeding partially explains why some dieters become stuck at a plateau after having lost the first 10 or so pounds of weight had failed. Nutrition, a compensatory reduction in the efficiency of energy use in response to overeating accounts for the difficulty experienced by very thin people who are deliberately trying to gain weight. Despite these modest compensatory changes in metabolism, regulation of food intake is the most important factor in the long-term maintenance of energy balance and body weight.

![FIGURE 17.2](image)

Compassion of a normal rat with a rat whose hypothalamus has been destroyed.

Several months after destruction of the classical satiety center in the ventromedial area of the hypothalamus, the rat on the right had gained considerable weight as a result of overeating compared to its normal littermate on the left. Rat-staining depressed in this area also display less grooming behavior, accounting for the weight appearance of the fat rat.

Food Intake is controlled primarily

by the hypothalamus.

Control of food intake is primarily a function of the hypothalamus. Classically, the hypothalamus is considered to have a pair of centers, or anorexic or satiety centers, located in the lateral hypothalamic regions. These anorexic centers, located in the lateral hypothalamic, one on each side, and another pair of satiety centers located in the ventromedial (anorexic) or lateral) area. Satiety is the feeling of being full. The functions of these areas have been characterized by a series of experiments that involve either destruction or stimulation of these specific regions. Stimulation of these centers results in the feeding, or appetite centers, which produce the feeling of being full (Figure 17.7). Thus, the feeding centers tell us to eat, whereas the satiety centers tell us when we have had enough. Although it is convenient to consider these specific areas as exciting and inhibiting feeding behavior, respectively, this approach is too simplistic. It is now known that complex systems of signals from the satiety centers control feeding and satiety. Multiple, highly integrated, redundant pathways cross over into and out of the hypothalamic areas involved in the control of food intake and maintenance of energy balance.

Even though food intake is adjust to balance changes in energy expenditure over a period of time, the brain is not only able to monitor energy intake and output, but also total body energy content. In fact, various blood-borne electrical fac-

ions that signal the body's nutritional state, such as how much fat is stored or how much glucose is available, are important in regulating food intake. Control of food intake does not depend on changes in a single signal but is determined by the integration of many inputs that provide information about the body's energy status. Multiple signals act together to ensure that feeding behavior is synchronized with the body's immediate and long-term energy needs. Some information is used for short-term regulation of food intake, helping to control usual meal size and frequency. Even so, over a 24-hour period the energy intake of a typical rat is matched by energy expenditure for that day. The balance between total caloric intake and total energy output is crucial, however, over longer periods of time. As a result, the total energy content of the body and, consequently, body weight remains relatively constant on a long-term basis. Thus energy homeostasis, that is, energy balance, is carefully regulated. Based on current evidence, the following regulatory factors are among those that contribute to the control of food intake and maintenance of energy balance (Figure 17.3).

The size of fat stores

Our notion of fat cells (adipocytes) in adipose tissue as merely storage space for triglyceride fat has undergone a dramatic change in the past decade with the discovery of their active role in energy homeostasis. Adipocytes secrete leptin, a hormone essential for normal body weight regulation (leptin means
Role of neuropeptide Y and melanocortins

Neuropeptide Y (NPY) is one of the most potent appetite stimulators ever found. NPY not only triggers various feeding behavior but also lowers energy expenditure by suppressing sympathetic nervous system output, thereby decreasing the metabolic rate. Thus, NPY promotes weight gain. Leptin suppresses food intake and increases metabolic rate in part by inhibiting hypothalamic output of NPY. On the other side of the coin, the loss of fat stores and the resultant reduction in leptin can lead to eating behaviors about increased NPY release. NPY, in turn, sets in motion actions that oppose the weight loss.

Melanocortins, a group of hormones traditionally known to be important in varying the skin color for the purpose of camouflage in some species, have been shown to exert an unexpected role in energy homeostasis. Melanocortin, most notably, melanocortin-stimulating hormone (MSH), inhibits the hypothalamus to decrease food intake. Melanocortins do not play a role in determining skin coloration in humans. Their importance in our species lies in part in toning down appetite in response to increased fat stores. Leptin stimulates the melanocortin system. Thus, leptin promotes weight loss by simultaneously inhibiting the appetite-enhancing NPY pathway and stimulating the appetite-suppressing melanocortin pathways.

But NPY and melanocortin may not be the final effectors in appetite control. Recent evidence suggests that these areacti-
molecules chemical messengers may in turn influence the release of neuropeptides in other parts of the brain that exert control over food intake.

Beyond the arcuate nucleus: Orexins and others

Two hypothalamic areas are richly supplied by axons from the NPY- and melanocortin-secreting neurons of the arcuate nucleus. These areas are the lateral hypothalamic area (LHA) and paraventricular nucleus (PVN). According to a recently proposed model, the LHA and PVN release chemical messengers in response to input from the arcuate nucleus neurons. These messengers are believed to act downstream from the NPY- and melanocortin neurons to regulate appetite. The LHA, the site of the classical appetite center, produces two closely related neuropeptides known as orexins, which are potent stimulators of food intake (orexin means "appetite"). In the proposed model, NPY stimulates and melanocortin inhibits the release of orexins, leading to an increase in appetite and greater food intake. By contrast, the PVN releases chemical messengers that decrease appetite and food intake. An example is corticotropin-releasing hormone, which, as its name implies, is better known for its role as a hormone. (You will learn more about this chemical's endocrine function in the next chapter.) According to the model, melanocortin stimulates and NPY inhibits the release of these appetite-suppressing neuropeptides.

In addition to the importance of neuropeptide signals in the long-term control of body weight, other factors are believed to play a role in controlling the timing and size of meals. In contrast to the key role of the hypothalamus in maintaining energy balance and long-term control of body weight, a region in the brain area known as the nucleus tractus solitarius (NTS) is thought to be the site that processes signals important in terminating a meal. The NTS receives afferent inputs from the digestive tract and elsewhere that signal satiety and also receives input from the higher hypothalamic neurons involved in energy homeostasis. We now turn our attention to the most important of these satiety signals (Fig 17-3).

The extent of gastrointestinal distension

Early proposals suggested that cues of emptiness or fullness of the digestive tract signaled hunger or satiety, respectively. For example, stimulation of gastric stretch receptors has been shown to suppress food intake. However, neural input arising from stomach distension plays a more important role in controlling the rate of gastric emptying than in signaling satiety (see p. 696). Researchers now believe that internal blood-borne signals reflecting the depletion or availability of energy-producing substances are more important than stomach volume in controlling the initiation and cessation of eating.

The extent of glucose use and insulin secretion

Satiety is signaled by increased glucose use, such as occurs during a meal when more glucose is available for use because it is being absorbed from the digestive tract. Conversely, after absorption of a meal is complete, and no new glucose is entering the blood, the resultant reduction in the cells' glucose use anesthetizes the sensation of hunger. The extent of glucose use appears more important in determining the timing of meals than in the long-term control of body weight.

A related mechanism, increased satiety in the blood sugar set point, involves a hormone secreted by the pancreas in response to rise in the concentration of glucose and other nutrients in the blood following a meal, stimulates cellular uptake and storage of glucose and other nutrients. Thus, the increase in insulin secretion that accompanies nutrient absorption and promotes increased glucose use is an appropriate satiety signal.

The level of cholecystokinin secretion

Cholecystokinin (CCK), one of the gastrointestinal hormones released from the duodenal mucosa during digestion of a meal, is an important satiety signal for regulating the size of meals. CCK is secreted in response to the presence of nutrients in the small intestine. Through multiple effects on the digestive system, CCK facilitates digestion and absorption of these nutrients (see p. 690). It is appropriate that this blood-borne signal, whose role in satiety is correlated with the amount of nutrients ingested, also contributes to the sense of being full after a meal has been consumed but before it has actually been digested and absorbed. We feel satisfied when adequate food to replenish the stores is in the digestive tract, even though the body's energy stores are still low. This explains why we stop eating before the ingested food is ready available to meet the body's energy needs.

Psychosocial and environmental influences

Thus far we have described somatosensory signals that automatically occur to control food intake. However, as with water intake, people's eating habits are also shaped by psychological, social, and environmental factors. Often our decision to eat or stop eating is not determined solely by whether we are hungry or full, respectively. Frequently, we eat out of habit (eating the same meal a day on schedule), or we eat out of frustration; the sense of hunger—satiety continuum or because of social customs (food often plays a peal role in entertainment, leisure, and business activities). Even well-established family pressure—"Clean your plate before you can leave the table"—can have an impact on the amount consumed.

Furthermore, the amount of pleasure derived from eating can reinforce feeding behavior. Eating foods with an enjoyable taste, smell, and texture can increase appetite and food intake. This has been demonstrated in an experiment in which rats were offered their choice of highly palatable human foods. They overate by as much as 70% to 80% and became obese. When the rats returned to eating their regular, monotonous, but nutritionally balanced rat chow, their obesity was rapidly reversed as these food intake was controlled once again by physiological drives rather than by hedonic urges for the taste offerings.

Stress, anxiety, depression, and boredom have also been shown to alter feeding behavior in ways that are unrelated to energy needs in both experimental animals and humans. People often eat to satisfy psychological needs rather than because they are hungry. Furthermore, environmental influences, such as amount of food available, play an important role in deter-
mining excess food intake. Thus, any comprehensive explanation of how food intake is controlled must take into account these voluntary eating acts that can reinforce or override the internal signals governing feeding behavior.

Obesity occurs when more kilocalories are consumed than are burned up.

Obesity is defined as excessive fat content in the adipose tissue; the arbitrary boundary for obesity is generally considered to be greater than 20% overweight compared to normal standards. Over half of the adults in the United States are overweight, and one-third are clinically obese. Obesity occurs when, over a period of time, more kilocalories are ingested as food than are used to support the body's energy needs, with the excess energy being stored in triglycerides in adipose tissue. The causes of obesity are many, and some remain obscure. Some factors that may be involved include the following:

- Disturbances in the leptin signaling pathway. Some cases of obesity have been linked to leptin resistance. For many overweight people, excess energy input occurs only during the time that obesity is actually developing. Some investigators suggest that the hypothalamic centers involved in maintaining energy homeostasis are "set at a higher point" in obese people. Thus, overweight people do not tend to maintain their weight lost at a higher set point than normal. Once obesity is developed, all that is required to maintain the condition is that energy input equals energy output. For example, the problem may be with fatty leptin receptors in the brain that do not respond appropriately to the high levels of circulating leptin from abundant adipose stores. Thus the brain does not detect leptin as a signal to turn down appetite until a higher set point (and accordingly, greater fat storage) is achieved. Instead of fatty leptin receptors, other disturbances in the leptin pathway may be at fault, such as defective transport of leptin across the blood-brain barrier or a deficiency of one of the chemical messengers in the leptin pathway.
- Lack of exercise. Numerous studies have shown that, on the average, fat people do not exert any more than thin people. One possible explanation is that overweight persons do not exercise but "underexerciser"--the "coast,pad, sit,nap syndrome. Very low levels of physical activity typically are not accompanied by comparable reductions in food intake.

For this reason, modern technology is partly to blame for the current obesity epidemic. Our ancestors had to exert physical effort to make a living. By comparison, we now have machines to replace much manual labor, remote controls to operate our machines with minimal effort, and computers that encourage long hours of sitting. We have to make conscious effort to exercise.

- Differences in the "buddy factor." "Overeater activity thermogenesis" (NOAE), or the "buddy factor," might explain some variation in fat storage among people. Those who engage in taping or other types of repetitive, repetitive physical activity have an additional number of kilocalories throughout the day without a conscious effort.

- Differences in extracting energy from food. Another reason why lean people and obese people may have dramatically different body weights despite consuming the same number of kilocalories may lie in the efficiency with which each collects energy from food. Studies suggest that leaner individuals tend to derive less energy from the food they consume, because they convert more of the food's energy into heat than into energy for immediate use or for storage. You example, slimmer individuals have more uncoupling proteins, which allow their cells to convert more of the nutrient calories into heat instead of fat. These are the people who can eat a lot without gaining weight. By contrast, obese people may have more efficient metabolic systems for extracting energy from food--a useful trait in times of food shortage but a liability when trying to maintain a desirable weight when food is plentiful.

- Hereditary tendencies. Often, differences in the regulatory pathways for energy balance--those governing food intake or those influencing energy expenditure--arise from genetic variations.

- Development of an excessive number of fat cells as a result of overfeeding. One of the problems in fighting obesity is that once fat cells are created, they do not disappear with dieting and weight loss. Even if a dieter loses a large portion of the triglyceride fat stored in these cells, the depleted cells remain ready to refill. Therefore, reduced weight gain after losing weight is difficult to achieve and discouraging for the dieter.

- The existence of certain endocrine disorders such as hyperthyroidism (see p. 706). Hyperthyroidism involves a deficiency of thyroid hormone, the main factor that regulates the BMR so that the body burns more calories in its killing state.
- An abundance of convenience, highly palatable, energy-dense, relatively inexpensive foods.

- Emotional disturbances in which overeating replaces other gratifications.

- A possible viral link. One intriguing new proposal links a relatively common cold virus to a propensity to become overweight and may account for a portion of the current obesity epidemic.

Despite this rather lengthy list, we know nothing about the causes and control of obesity; it is still rather limited, as evidenced by the number of people who are constantly trying to stabilize their weight at a more desirable level. It is important from an aesthetic viewpoint to be lean, but obesity, especially of the android type, can predispose an individual to illness and premature death from a multitude of diseases. (To learn about the differences between android and gynoid obesity, see the accompanying boxed feature, p. 670.) (Look at Exercise Physiology.)

I People suffering from anorexia nervosa have a pathologic fear of gaining weight.

The converse of obesity is anorexia nervosa, a disease or disturbed eating behavior that results in an abnormally low body weight. This disorder is characterized by an intense fear of gaining weight, which is not just based on a false perception of being overweight. The patient may engage in self-induced starvation by drastically reducing food intake or by purging. Purging involves vomiting or the use of laxatives or diuretics to expel food from the stomach. The patient may also exercise excessively. The symptoms of anorexia nervosa include extreme weight loss, amenorrhea (absence of menstruation), and purging behavior.

Energy Balance and Temperature Regulation

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